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Myelodysplastic Syndrome With Erythroid Hypoplasia/Aplasia: A Case Report and Review of the Literature

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Myelodysplastic syndrome (MDS) with erythroid hypoplasia/aplasia has not yet been clearly defined, and in most patients it is mistaken for acquired pure red cell aplasia (PRCA). We report a patient with severe transfusion-dependent anemia (Hb 6.9 g/dl) and reticulocytopenia. WBC and platelet counts were normal. Bone marrow examination showed a marked trilineage dysplasia and a low percentage of erythroid precursors (3%). A diagnosis of MDS (refractory anemia according to FAB classification) with erythroid hypoplasia/aplasia was made. Repeated cytogenetic analysis of bone marrow showed normal karyotypes. Moreover, serial IgM serology and DNA analysis of the patient's sera for B19 parvovirus were negative. Other conditions known to be associated with erythroid aplasia were also absent. The patient failed hematinics and prednisone therapy. He next received r-HuEPO (200 U/kg three times weekly). This form of therapy achieved a rapid and complete erythroid response. He has remained in complete erythroid response after a 7-month period on maintenance therapy of 100 U/kg three times weekly. A review of the literature revealed only 15 well-documented cases of MDS with erythroid hypoplasia/aplasia. All had morphological evidence of myelodysplasia. These patients were predominantly elderly males, all required regular packed red cell transfusions, and had an unfavorable prognosis, mainly because of a high rate of blastic transformation (frequently preceded by a myeloproliferative phase). The mechanism of erythroid hypoplasia in this subgroup of MDS remains uncertain. However, laboratory and clinical data suggest the existence of an intrinsic stem cell defect. None of the patients received hematopoietic growth factors. To our knowledge, our patient is the first case of MDS with erythroid hypoplasia where r-HuEPO was successfully attempted. The description of more cases is necessary to delineate the value of r-HuEPO therapy in this rare variant of MDS. Am. J. Hematol. 58:319–325, 1998. © 1998 Wiley-Liss, Inc.

Key words: myelodysplastic syndrome; erythroid hypoplasia; r-HuEPO

INTRODUCTION

Myelodysplastic syndrome (MDS) with erythroid hypoplasia/aplasia is a rare form of myelodysplasia. Patients present with severe anemia, reticulocytopenia, and paucity of recognizable erythroid cells (2 to 5%) in bone marrow associated with some evidence of intrinsic stem cell defect (e.g., bilineage or trilineage dysmorphic abnormalities, thrombocytopenia, neutropenia) [1–5]. The exact incidence of MDS with red cell hypoplasia/aplasia is hard to establish because of the overlap between this entity and acquired pure red cell aplasia (PRCA). In a series of 360 cases of MDS diagnosed in a single institution over a 10-year period, 0.6% were found to have MDS with erythroid hypoplasia/aplasia [6]. In addition to erythroid hypoplasia, bilineage or trilineage dysplasia in a high percentage of cells (more than 20%) of the respective lineage is the critical determinant for the recognition of this entity.[1] The pathophysiology of red cell hypoplasia/aplasia in these cases remains uncertain, although in vitro culture studies and clinical data suggest

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the existence of an intrinsic defect of maturation and proliferation of erythroid precursors as part of the myelodysplastic disorder [5].

No effective treatment has yet been reported and most patients require repeated transfusions with a subsequent increased risk for developing haemosiderosis. A number of trials on the use of r-HuEPO in a range of MDS have now been performed and the results have been generally disappointing, with an overall erythroid response rate of 16% [7]. Considerating the relatively low response rate, the identification of pre-treating responding patients is important in order to avoid potentially expensive but ineffective therapy.

We hereby report the first case of an MDS patient with progressive red cell hypoplasia successfully treated with r-HuEPO. We will also review the clinicopathological features of the MDS with erythroid hypoplasia/aplasia reported in the literature.

CASE REPORT (TABLE I, CASE 16)

A 41-year-old man was referred to our department in November 1995 because of moderated anemia. He complained of fatigue and weightlessness. On admission, physical examination was normal except for pallor. Peripheral blood cell count was as follows: Hb 9.7 g/dl, MCV 113 fl, MCH 37 pg, MCHC 36 g/dl, platelets 314 $\times 10^9$/1, leucocytes 6.54 $\times 10^9$/1 (differential count: neutrophils 20.4%, lymphocytes 60.6%, monocytes 13.7%, eosinophils 3.1%, basophils 2.2%). The absolute reticulocyte count was 18 $\times 10^9$/1. The blood smear showed marked anisocytosis, spherocytosis, macrocytosis, and elliptocytosis. Biochemical tests were all within normal ranges except a slightly elevated LDH (412 U/1). Serum iron level and saturation of transferrin were increased (180 μg/dl and 67%, respectively). Serum ferritin was increased (170 ng/ml). There was no vitamin B12 deficiency (serum level: 711 pg/ml; normal 180–1130 pg/ml), or folic acid deficiency (serum level: 4.5 ng/ml; normal 2.5–17 ng/ml). Coombs test was negative and erythrocytic enzymes (glucose-6-phosphate dehydrogenase and pyruvate kinase) were normal. Serological tests for CMV, heterophilic antibodies, HIV, HSV, and hepatitis A and C were negative. Testing of serum for antibodies against hepatitis B showed a past infection. A chest X ray and computed tomography of the thorax and abdomen were normal.

Bone marrow aspirate and biopsy specimens showed a hypercellular bone marrow with 1.2% blasts, 5.2% promyelocytes, 16.4% myelocytes, 34.6% metamyelocytes, and mature neutrophils, 7% eosinophils, 21.8% lymphocytes, 3.8% monocytes, 1% plasmocytes, and 10% erythroblasts. Numerous dysplastic features were observed in the three lineages. The few erythroid cells were young and displayed marked dyserythropoietic changes: karyorrhesis, megaloblastosis, nuclear budding, internuclear bridging, and punctate basophilia. Giant pronormoblasts were absent. The Prussian Blue stain showed 2% ring sideroblasts. Granulopoiesis was often hypogranular. Auer rods were not observed. Abnormal thrombopoiesis was also present with an increased number of megakaryocytes with bilobed nuclei and nuclear-cytoplasmic asynchrony. Bone marrow biopsy did not detect an increase of reticulin fibrosis. Figure 1 shows May-Grünwald-Giemsa stained smear of bone marrow specimen from this patient. The smears exhibited varying signs of erythroid dysplasia (e.g., nuclear abnormalities and basophilic stippling) and hypo- or agranular myeloid cells. Conventional cytogenetic analysis performed on bone marrow cells showed a normal karyotype (46 XY). Ham's test was negative. Flow cytometric analysis for GPI-anchored proteins on peripheral blood cells (red blood cells, neutrophils, and lymphocytes) consistently showed a normal expression of GPI-linked proteins. Serological tests (IgG and IgM) and DNA analysis of patient's serum (polymerase chain reaction technique) for human parvovirus B19 did not show any evidence of persistent infection with this virus. Serum immunoelectrophoresis and immunoglobulins levels were normal. Antinuclear antibodies, anti-DNA antibodies, and antithyroid antibodies were negative. Flow cytometric immunophenotyping of the peripheral blood and bone marrow showed a normal distribution of lymphocyte subsets.

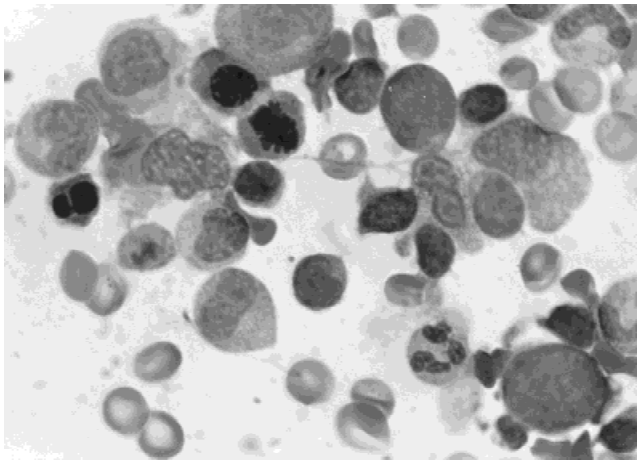

Fig. 1. Bone marrow smear at the time of diagnosis showed trilineage dysplasia consistent with MDS. Bizarre nuclear profiles with increased pyknosis in erythroblasts are noted. Together with a red cell with basophilic stippling, a giant platelet with clumped granules is seen on the left side. One myeloblast is present, and some hypogranular myeloid cells may also be seen. May-Grünwald-Giemsa ×1,000.

A diagnosis of MDS with erythroid hypoplasia/aplasia was made, and the patient received a course of hematin-

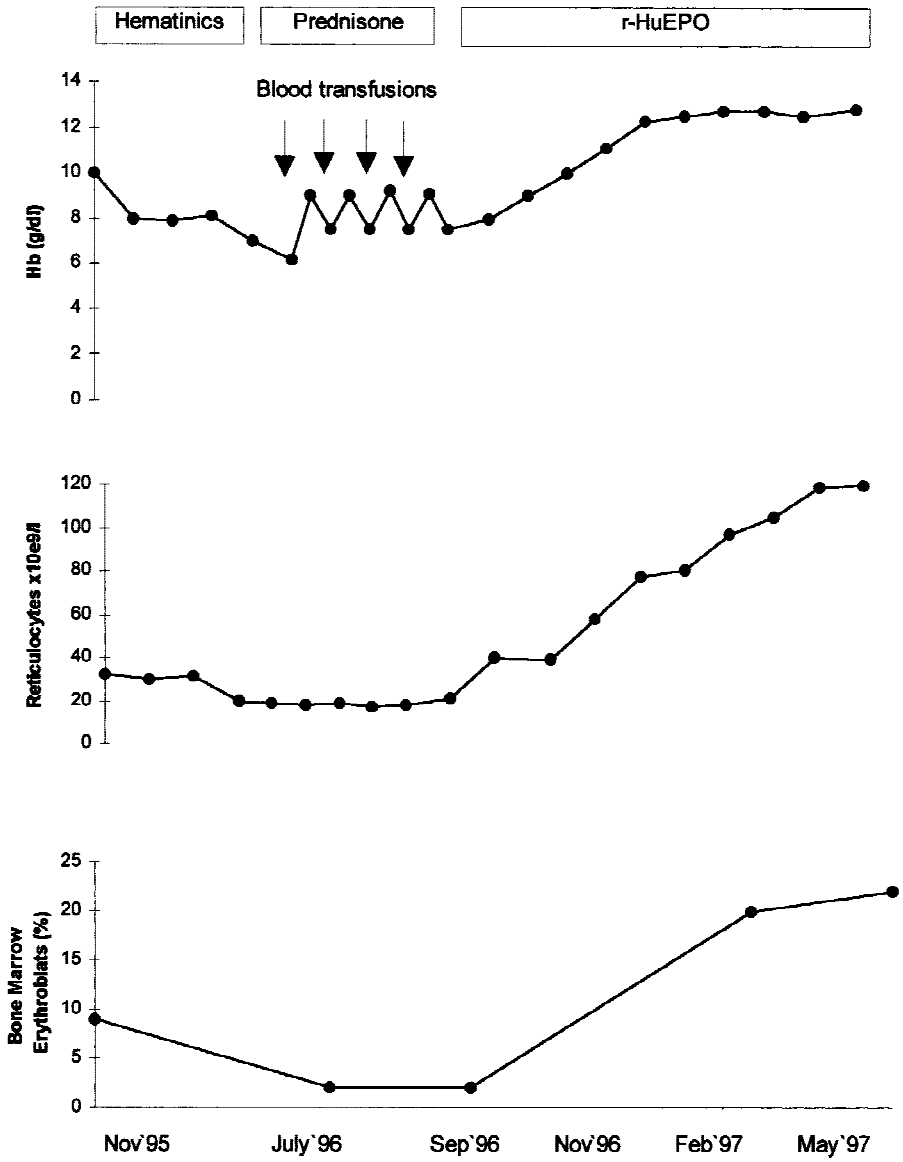

Fig. 2. Hematological data and treatment of our case (see text).

ics (folic acid, vitamin B_{12}, pyridoxine, and thiamine). There was no response to this treatment. In July 1996, hemoglobin was 6.9 g/dl and prednisone (1 mg/k/d) was then started. However, the patient became progressively more anemic and dependent on packed red cell transfusions. In August 1996, a repeat bone marrow showed virtually no erytroblasts (3% of all nucleated marrow cells) and more marked trilineage dysplasia. Cytogenetic studies on the bone marrow remained normal and subsequent serological tests for human parvovirus B19 were negative. Endogenous serum EPO level was 110 mU/ml (normal 10–21 mU/ml). At the time the EPO sample was drawn, hemoglobin concentration was 8.2 g/dl. Prednisone was finally stopped in September 1996. After informed consent was obtained, a trial of r-HuEPO (Eprex, Janssen-Cilag) was started subcutaneously in October 1996 at a dose of 200 U/kg three times weekly. The patient's condition gradually improved and became transfusion-indepent after 3 weeks of treatment. Hemoglobin and reticulocyte response were excellent (see Fig. 2). After November 1996, he was in excellent condition, working full time. Side reactions to the r-HuEPO treatment were not observed. In February 1997, a normal hemogram was found with Hb 14.5 g/dl, MCV 110 fl, platelets 225×10^9/l, WBC 7.2×10^9/l, and reticulocytes 112×10^9/l. The bone marrow showed an increased cellularity with a myeloid:erythroid (M:E) ratio of 3.7:1. There were 20% erythroblasts and 2% blasts. Marked trilineage dysplasia was found. The karyotype in culture remained normal in all the 20 metaphases. In April 1997, the dose of r-HuEPO was reduced at 150 U/kg/d three times a week, and the patient sustained a normal hemo-

TABLE I. Summary of Clinical Data, Modes of Treatment, and Outcome of 16 Cases Analyzed (Including Ours) *

		Bone marrow at presentation		Bone marrow (subsequently)					
Case no/age/sex	Reference	MDS subtype	Karyotype	Time (months)[a]	MDS subtype	Karyotype	Therapeutic response	Clinical outcome	Survival (months)
1/49/M	[8]	RA Blasts: NR EP: hypoplastic	Normal	11	Atypical MPD Blasts: 10% EP: absence	Not done	ANDR → NR, C-RA → NR, LD-AraC → NR	Alive. Progression to ANLL	60+
2/62/M	[8]	RA Blasts: NR EP: hypoplastic	Normal	48	Atypical MPD Blasts: 5–10% EP: absence	Not done	ANDR → NR, LD-AraC → NR, C-RA → NR	Died of blastic transformation	60
3/75/F	[8]	RA Blasts: NR EP: hypoplastic	Normal	6	Atypical MPD Blasts: NR EP: absence	Not done	P → PR (relapse after taper)	Died of ANLL (monocytic)	30
4/66/M	[9]	PRCA EP: absence	Not done	4	CMML Blasts: 6% EP: absence	Normal	ANDR → NR, P → NR	Alive and transfusion-dependent	4+
5/76/M	[9]	PRCA EP: absence	Not done	3	CMML Blasts: 6% EP: absence	Normal	Not reported	Not reported	Not reported
6/69/M	[10]	RA Blasts: NR EP: 3.5%	Not done	6	Atypical MPD Blasts: NR EP: absence	Normal	P → NR, 6MP → NR	Died of carcinoma of bronchus	24
7/83/F[b]	[10]	RAEB Blasts: 6% EP: hypoplastic	Not done	12	RAEB Blasts: NR EP: decreased	Normal	P → CR (relapse after taper)	Alive and transfusion-dependent	36+
8/67/M	[11]	CMML Blasts: NR EP: 2%	Normal	5	Blastic transformation	Not done	P → PR, 6MP → NR, CY → NR	Died of blastic transformation	5
9/82/F	[6]	RAEB Blasts: 9% EP: 10%	Not done	10	RAEB Blasts: 17% EP: 1%	Not done	Not reported	Died of sepsis	11
10/78/F	[6]	RARS Blasts: NR EP: 34%	Not done	53	Atypical MPD Blasts: 8% EP: 1%	Not done	Not reported	Died of sepsis	56
11/81/F	[6]	CMML Blasts: 2% EP: <1%	Not done	2	Atypical MPD Blasts: 2% EP: 3%	Not done	Not reported	Died of blastic transformation	7
12/74/M	[6]	RA Blasts: NR EP <1%	Not done	7	RA Blasts: NR EP: 37%	Not done	P → PR	Alive and transfusion-independent	22+
13/58/F	[6]	RA Blasts: NR EP: 1%	Not done	6	RA Blasts: NR EP: 23%	Not done	Not reported	Alive and transfusion-dependent	28+
14/87/M	[6]	RA Blasts: NR EP: 1%	Not done	5	RA Blasts: NR EP: 1%	Not done	Not reported	Died of unrelated causes	9

TABLE I. Continued

Case no/age/sex	Reference	Bone marrow at presentation		Bone marrow (subsequently)			Therapeutic response	Clinical outcome	Survival (months)
		MDS subtype	Karyotype	Time (months)[a]	MDS subtype	Karyotype			
15/74/M	[12]	RA Blasts: 2.8% EP: 1.5%	Normal	—	Not done	Not done	P → NR	Alive and transfusion-dependent	11+
16/41/M	Our case	RA Blasts: 1.2% EP: 10%	Normal	8	RA Blasts: 1.5% EP: 3%	Normal	Hematinics → NR, P → NR, r-HuEPO → CR	Alive and transfusion-independent	18+

*ANLL, acute nonlymphocytic leukemia; ANDR, androgens; CR, complete erythroid response (if haemoglobin became normal); C-RA, cis-retinoic acid; CY, cyclophosphamide; EP, erythroid precursors; LD-AraC, low dose cytosine arabinoside; 6-MP, 6-mercaptopurine; MPD, myeloproliferative disorder; NR, absence of erythroid response; NR, not reported; PR, partial erythroid response (if need for red cell transfusions ended); P, prednisone.

[a]Indicates months from presentation.

[b]Patient with mycosis fungoides.

gram with maintenance therapy at the time of the last follow-up (18 months). At the time of writing, peripheral blood showed Hb 14.8 × 10^9/l and reticulocytes 105 × 10^9/l. All clinical specimens were obtained after informed consent from the patient.

SUMMARY OF DATA FROM THE LITERATURE

After a careful literature search, we have identified 15 well-documented additional cases of MDS with erythroid hypoplasia/aplasia (Table I) [6,8–12]. There was a male predominance (male to female ratio of 3:1) with a mean age of 70 years (range 41–87 years). One patient (no. 1) had a history of prior exposure to toxic agents (trichloretylene). In another patient (no. 7), polymyalgia rheumatica and mycosis fungoides were detected during the course of the disease. All patients had bone marrow dysplasia in at least two of the hematopoietic cell lines to allow the clinical diagnosis of MDS. FAB subtypes were refractory anemia (RA) in 9 (56%), chronic myelomonocytic leukaemia (CMML) in 4 (25%), refractory anemia with excess blasts (RAEB) in 2 (12.5%), and refractory anemia with ringed sideroblasts (RARS) in 1 (6.2%). The most common symptom presented was the anemic syndrome. Cytogenetic studies of bone marrow cells were performed on 9 patients (nos. 1–8, and 15), all 9 cases had normal karyotypes.

Burst forming unit-erythroid (BFU-E) and colony forming unit-erythroid (CFU-E) frequencies were determined in 4 patients (nos. 3, 4, 5, and 8). None of these patients showed any growth of erythroid colonies, a pattern observed in myelodysplasia. In vitro coculture studies were performed only in one case (no. 5). In this single case, normal marrow cells from a healthy volunteer cultured with and without plasma from the patient showed no evidence of antibody mediated inhibition of erythropoiesis. However, in this patient, coculture studies to investigate T-cell mediated suppression of erythropoiesis were not performed. In 2 patients, human parvovirus (HPV) B19 tests were made showing absence of HPV B19 infection. In the remaining 13 patients, no HPV B19 tests were performed since clinical data did not support such infection. Finally, an immunologic disorder (mycosis fungoides) was only found in one patient (no. 7). No other conditions known to be associated with acquired PRCA were found in 14 out of 15 patients analyzed.

All patients were transfusion-dependent. Patients often received more than one therapy. Seven patients received a short course of steroids (nos. 3, 4, 6, 7, 8, 12, and 15) and 4 of them (nos. 3, 7, 8, and 12) became transfusion independent. All these patients relapsed after steroids were stopped, except patient no. 12 who had a sustained partial erythroid response without maintenance therapy. Other forms of therapy including androgens (3 cases), low-dose cytosine arabinoside (2 cases), cis-retinoic acid

(2 cases), 6-mercaptopurine (2 cases), and cyclophosphamide (1 case) were attempted without success.

Clinical follow-up was reported in 14 patients. The median survival of these 14 patients was 27 months (SE: 0.15). Of the 14 patients, 8 have died because of blastic transformation (nos. 2, 3, 8, and 11), sepsis (nos. 9 and 10), and unrelated causes (nos. 6 and 14). The chance of leukemic transformation was 35.7%. Among the 5 patients with blastic transformation (nos. 1, 2, 3, 8, and 11), time of evolvement into acute myeloid leukemia ranged from 7 to 60 months. The development of blastic transformation did not correlate with FAB subtype, since 3 patients (nos. 1, 2, and 3) had RA and 2 patients (nos. 8 and 11) had CMML prior to acute transformation. It is interesting to note that, among the 5 patients with blastic transformation, 4 patients (nos. 1, 2, 3, and 11) had a myeloproliferative phase (rising peripheral blood neutrophil, platelet, and monocyte counts) prior to evolving into a blastic phase. In another 2 patients (nos. 6 and 10) a myeloproliferative phase was also observed prior to an increase in blast cells in the bone marrow.

DISCUSSION

MDS with erythroid hypoplasia/aplasia is a rare form of myelodyplasia, with only 16 well-documented cases reported in the literature including ours. Patients with this disorder were predominantly elderly males at presentation, all requiring regular blood transfusions, and with an unfavorable prognosis because of a high risk of blastic transformation. In contrast to primary acquired PRCA, steroids were no longer helpful because of the intrinsic stem cell defect. A main finding in the present article was that we provided the first case of MDS with erythroid hypoplasia/aplasia where r-HuEPO was attempted. This form of therapy achieved a complete erythroid response.

Myelodysplastic disorders characteristically exhibit a high number of erythroid precursors in the marrow. However, a minority do have paucity (less than 5%) of recognizable erythroid cells in bone marrow. Within this group, most of the patients with erythroid hypoplasia have the so-called MDS with erythroid hypoplasia/aplasia [4,5], and the remaining ones fulfill the diagnostic criteria for 5q-syndrome [13]. The distinction between these subtypes of MDS may be important to define physiologies of MDS and correlate these with therapeutic responses. All patients with MDS and red cell hypoplasia/aplasia who were karyotyped (10/16) showed normal karyotypes. Thus, it is likely that no patients with 5q-syndrome were included in our case study.

The incidence of MDS with erythroid hypoplasia/aplasia is probably underestimated because in most patients it is often mistaken for acquired PRCA. In a recent series of 40 patients with acquired PRCA, 17% of them were found to have MDS with erythroid hypoplasia/aplasia [5].

The mechanism of erythroid hypoplasia in this subgroup of MDS patients remains uncertain. A number of autoimmune diseases has been suggested to occur rather frequently in MDS [14]. However, clinical data suggest that an autoimmune etiology is unlikely because most patients (15/16) from our case study of MDS with erythroid hypoplasia/aplasia did not have immunologic disorders known to be associated with autoimmune red cell aplasia, and, only 1 (no. 12) out of 8 patients showed a sustained response to steroids. In addition, it has recently been described that in almost 95% of patients with immunologically mediated PRCA, BFU-E had the ability to proliferate in vitro but not in vivo, and this pattern of BFU-E growth was also predictive of clinical response to immunomodulating therapy [5]. These results are compatible with data previously reported by Lacombe et al. [15]. In contrast to the cases with immune-associated PRCA, all cases (7 out of 7) with PRCA associated to myelodysplastic features showed an absent BFU-E growth, and in all 7 cases the anemia was refractory to immunosuppressive therapies [5]. In our case study, 4 out of 4 patients who had marrow culture studies showed a poor BFU-E and CFU-E growth. Thus, this in vitro growth pattern suggests erythroid dysplasia rather than autoimmune erythroid hypoplasia. Finally, our literature review does little to elucidate the role of HPV B19 in the pathogenesis of red cell hypoplasia/aplasia in this form of MDS. Only 2 of these patients had IgM serology and/or DNA studies for HPV, and none of them was positive. The aforementioned observations suggest that these individuals had an intrinsic stem cell defect (myelodysplasia) and BFU-E were unable to mature in vivo and in vitro because of this intrinsic defect.

Our case and those reported in the literature indicate that this is not a morphologically homogeneous group of patients, because, although they all had erythroid hypoplasia/aplasia and prominent bilineage or trilineage dysplasia, 9 presented RA, 4 CMML, 2 RAEB, and 1 RARS. Moreover, 2 cases (nos. 4 and 5) presented as selective erythroid aplasia that 3 and 4 months later evolved into CMML, respectively; similar cases have been reported previously [15]. Interestingly, 6 cases (35.7%) of our case study of 16 patients evolved into a myeloproliferative phase with both dysplastic and proliferative features. This evolution of myelodysplasia in which myeloid maturation becomes proliferative rather than ineffective is rare (usually under 4% of patients) in other states of MDS [16].

The treatment with cytotoxic or differentiation-inducing agents in our case study of 16 patients has not been effective. Only one patient responded to corticosteroids in terms of discontinuation of transfusion requirements. None of the patients (except ours) received he-

matopoietic growth factors. In our case, the anemia was refractory to common hematinics and steroids, and transfusions were regularly required (Fig. 1). Because of the need for frequent transfusions, treatment with r-HuEPO was commenced at a high dose. There was a gradual increase in reticulocyte count (up 112 × 10^9/l) and the hemoglobin reached normal levels within 5 months. At the time of maximal erythroid response to r-HuEPO treatment, a marked dyserythropoiesis was observed in all marrow erythroid precursors from our patient. This feature suggests that the beneficial effect of r-HuEPO in our patient was by stimulation of proliferation and maturation of the myelodysplastic erythroid clone but not by stimulation of residual normal erythroid precursors. Overall 15 to 20% of patients with MDS respond to r-HuEPO. Although factors predicting response are not well established, our patient had some negative predictive factors (transfusion-dependent anaemia and erythroid hypoplasia in bone marrow). However, an excellent erythroid response was observed. Therefore, consideration should be given to using r-HuEPO earlier to treat anemia in these rare subgroup of MDS patients.

Whether MDS with erythroid hypoplasia/aplasia has any prognostic significance is premature because of the small number of patients reported. It is of interest to note that our study group showed several favorable prognostic factors for patients with MDS such as frequent normal karyotype (although 6/16 patients were not karyotyped), predominance of RA, absence of pancytopenia, and a good risk score according to International, Spanish, or Bournemouth prognostic systems (data not shown) [17–19]. However, an unexpectedly poor prognosis was observed (median survival 27 months), especially because of a high rate of blastic transformation. Further information is necessary before making general statements about a poor prognosis for this variant of MDS.

CONCLUSIONS

MDS with erythroid hypoplasia/aplasia is a rare form of MDS (0.6% of all cases) [6]. Although it is difficult to draw conclusions on the basis of a literature review of only 16 cases, we found that this entity is associated with a greater male sex preponderance, older age, high risk of transformation to acute leukemia (frequently preceded by a myeloproliferative phase), and a lower survival. Conventional therapies are ineffective in the management of this entity. The only patient (our case) who received treatment with r-HuEPO achieved a complete erythroid response. However, a single patient treated successfully with r-HuEPO does not mean that all patients with red cell hypoplasia/aplasia will respond. The description of more cases is necessary to confirm whether MDS with erythroid hypoplasia/aplasia represents a subgroup of MDS where r-HuEPO is specifically indicated. All these data support that MDS with erythroid hypoplasia/aplasia might be regarded as a distinct clinico-pathological entity. Identification (by FISH techniques and molecular analysis) of a cryptic chromosomal abnormality, undetectable at karyotypic level, might confirm this proposal. Further studies are needed to corroborate whether there is a relationship between this morphologic entity and specific citogenetic changes.

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